REMARKS

Claim 31 has been amended to obviate the rejection under 35 U.S.C. § 112, paragraph 2. Claim 31 has been clarified to note that it is the composition "defined in" claim 20 that is reconstituted. Accordingly, this basis for rejection may be withdrawn. Also, claim 27 has been made dependent on claim 20 for conciseness.

Applicants wish to call the attention of the Examiner to the enclosed decision of the Board of Patent Appeals and Interferences in the parent application, US 09/888,734, (Exhibit D).

Obviousness

The sole remaining basis for rejection (other than double patenting) is under 35 U.S.C. § 103 applied to all claims over Curtis, *et al.*, U.S. 5,824,780 in view of Livesey, *et al.*, U.S. 5,364,756 and Lee, *et al.*, EP 0314095.

The claims in this application are directed to a composition of Factor VIII which is stable without refrigeration and which contains a stabilizing amount of trehalose and no albumin. This is directly contrary to the teaching of Curtis, for example, which suggests that even lyophilized activated Factor VIII must be stored at low temperatures (*see* column 5, lines 39-43). Further, this considerable contribution to the art does not appear to be addressed in the rejection which focuses on lyophilization. The importance of eliminating albumin from Factor VIII compositions is amply illustrated by experience in the clinical context. The albumin-free Factor VIII composition developed according to the present application which comprises trehalose as a stabilizing agent (Advate®) has largely replaced the albumin-containing Factor VIII composition, Recombinate®. By the end of 2005, 70% of European patients using Recombinate® had switched to Advate®. In the UK, all patients previously using Recombinate® had converted to Advate®. Advate® is the first and

only Factor VIII therapy made available without human- or animal-derived proteins. Advate® has been approved by the Food and Drug Administration, and has a large market worldwide. Thus, the significance of the present invention is recognized in the marketplace.

Enclosed (Exhibit E) is a PubMed abstract of a publication in 2003 (*Drugs RD* (2003) 4:366-368) reporting that Baxter Healthcare licensed the technology claimed herein for $1,000,000 with additional milestone payments of $2,000,000, attesting to the commercial significance of this technology. Also enclosed (Exhibit F) is a review by Wang, *et al., Int. J. Pharm.* (2003) 259:1-15. Page 6 notes that "the stability of lyophilized Factor VIII products depends largely on the presence of protein stabilizers." It goes on to explain that Kogenate® and Recombinate® contain human serum albumin (HSA) and that these products are fairly stable. However, the stability of HSA-free formats called Kogenate® PS and ReFacto® is described as "significantly compromised." As noted, "an optimal formulation for lyophilized Factor VIII still needs to be explored with the goal of achieving a comparable stability that is afforded by HSA." Thus, the present invention clearly meets a long-felt need.

Turning now to the specific grounds for rejection advanced by the Office, as the Office has constructed the rejection by discussing the documents individually, applicants will begin their discussion in the same manner.

As Curtis is the primary document, this will be discussed first. In applicants' view, Curtis is entirely irrelevant to the claims at issue. Any description of methods of stabilization in Curtis are applied to a different protein from that which is the subject of the present claims. Curtis concerns, to the extent it contains any description of stabilization at all, stabilization of activated Factor VIII. The present claims are directed to methods and compositions for stabilization of native Factor VIII,

a different protein with different characteristics. As the Office is aware, evidence is of record in the parent application herein attesting to the differing nature of these proteins. For the convenience of the Office, the declarations of Sam L. Helgerson, E. G. D. Tuddenham, and Dr. Francis E. Preston are included with this response (Exhibits A, B and 12), as well as a copy of the article by Vehar, G. A., *et al., Nature* (1984) 312:337-342 (Exhibit C). This expert testimony and description in a peer reviewed journal clearly establish that native Factor VIII and activated Factor VIII are different proteins with different characteristics. The Office might as well have cited a document describing stabilization of asparaginase or tissue plasminogen activator and asserted its relevance.

In addition, Curtis does not describe a process for stabilizing a dried composition even of activated Factor VIII. The section noted by the Office in column 5, at lines 29-43, to the extent it refers to stabilizing agents addresses stabilizing agents for protection during activation and purification, not of a dried composition. Further, the description at line 41 states that "the protein can be lyophilized and stored at reduced temperatures until the protein is to be administered..." This is in direct contradiction to the requirement of the present claims that the composition resulting from the process of claim 27 and claimed in claim 20 must be stable without refrigeration.

As to claim 4 of Curtis, where human serum albumin and trehalose are assertedly listed in the alternative, this claim not only applies only to activated Factor VIII, not the native Factor VIII of the present invention, but fails to address a dried composition of anything. Claim 5, which at least concerns lyophilization, is dependent on claim 1 (not claim 4) and claim 1 does not suggest the presence of trehalose.

In short, Curtis, the primary document made the basis for rejection, is not even relevant to the invention as claimed. For that reason alone, the rejection should be withdrawn.

Unlike Curtis, documents that do, in fact, describe compositions of Factor VIII uniformly require the presence of albumin as a stabilizing agent. These documents are also of record in the parent case and copies are included with this response for the convenience of the Office. They are as follows:

1. An Alpha Therapeutic Corporation advertisement in the February 15, 2000, issue of the Journal *Blood*, stating that all recombinant Factor VIII products contain albumin which is necessary for preserving the factor proteins;

2. An excerpt from the 1999 Physicians' Desk Reference describing the Helixate® recombinant Factor VIII product which is stabilized with albumin and lyophilized;

3. U.S. patent No. 4,361,509 which describes, at column 10, lines 1-3, the necessity to include human serum albumin in Factor VIII prior to storage;

4. The expert declaration of Dr. Allen Mackenzie which states that Factor VIII preparations were believed to require albumin in order to stabilize the Factor VIII;

5. A North Carolina Hemophilia Center website extract from 2002, stating that human albumin is used as a stabilizer for Factor VIII;

6. An article by Brownlee, *et al.*, stating that the purified Factor VIII is stabilized by the addition of human albumin;

7. A web-page from the Puget Sound Blood Center of November 1999, stating that recombinant Factor VIII concentrates are stabilized by adding pasteurized human serum albumin;

8. A web-page from Emory Health Sciences dated October 10, 2000, verifying that recombinant Factor VIII, at that time, was stabilized with human serum albumin;

9. A web-page from the National Hemophilia Foundation website of January 10, 2001, stating that ReFacto® is the first recombinant human Factor VIII product formulated without human serum albumin;

10. U.S. patent 6,171,825 filed 4 September 1998, indicating the desirability of ridding Factor VIII preparations from albumin;

11. WO 94/07510 stating that the use of albumin for stabilization of Factor VIII is currently used in all highly purified Factor VIII products on the market; and

12. The Declaration of Francis E. Preston which attests to the common use of albumin as a stabilizer which is undesirable but considered necessary.

The Lee document cited in the present Office action, while describing lyophilization of Factor VIII in the absence of albumin substitutes a high ionic strength medium rather than trehalose; as set forth in the present Example 1, high ionic strength results in instability.*

No document cited by the Office suggests including trehalose as a stabilizer in order to avoid the necessity for including albumin in a composition of dried native Factor VIII.

The Office recognizes that Curtis is necessary to the rejection. There is no assertion that Livesey taken alone or that Livesey in combination with Lee defeats patentability of the present claims. As Curtis is an inappropriate document, applicants believe the rejection should be withdrawn as failing validly to include an assertedly necessary document. However, for completeness, the disclosure of Livesey, is discussed below.

The Office first notes that claim 17 of Livesey indicates that Livesey's process can be applied to Factor VIII. But Livesey's process is that of claim 1. Claim 1 requires preparing a cryosolution with suspension of biological material (the cryosolution comprising a buffer, a

cryoprotectant and a biological material), nebulizing it, cooling the resulting microdroplets to a temperature much lower than normal freeze-drying temperatures so that certain types of ice are formed and spraying the microdroplets against a solid cryogenic surface, continuously removing the splattered microdroplets which have become solid at this point and then drying them. The frozen cryosolution is removed from the cryogenic surface and then dried (*see* column 5, lines 63, *et seq.*). Drying may be achieved by conventional freeze-drying (*i.e.* lyophilization) or by using a molecular distillation dryer (*see* column 6, lines 7, *et seq.*).

The description of cryoprotectants begins in column 9 at line 5 and lists, among other things, trehalose, human serum albumin "and combinations thereof" (line 11). Skipping over this, the Office quotes lines 16-32 to a discussion of "dry protectant compounds." No dry protectant compound is required in claim 1 from which claim 17 depends. (The addition of a dry protectant appears only in claim 3.) Dry protectants are never used alone in Livesey's method. The further discussion, beginning at line 33 appears also to be ignored. This discussion lists, specifically, human serum albumin plus trehalose as cryoprotectants alone or in combination with other cryoprotectants or additional components (for example, dry protectants). Reading the relevant section from column 9, lines 5-39 would not convey to the skilled artisan that trehalose alone could be used in the absence of albumin as the cryoprotectant in claim 1 from which claim 17 depends.

In summary, Livesey's process requires a cryoprotectant. Nothing in the discussion of cryoprotectants suggests trehalose can be used alone.

Similarly to the discussion of Curtis, the knowledge of the skilled artisan must be taken into account in how Livesey would be interpreted. Just because trehalose and Factor VIII are mentioned in the same document does not lead to the conclusion that trehalose can be used as a stabilizer in the

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* In any event, Lee is cited for its teaching of Ca^{+2} and is thus properly included in a rejection only of claim 23.

absence of albumin, when the artisan already knows that albumin is required. There is nothing in the document which would contravene that understanding. Claim 1 which describes the process from which claim 17, naming Factor VIII, depends requires only a cryoprotectant. The quoted section of the application does not involve cryoprotectants but dry protectants. Where cryoprotectants are discussed, combinations of the listed protectants are specifically mentioned.

The Office point to the only example of Livesey that mentions trehalose, Example 5. Example 5 is concerned with stabilizing an entire virus for vaccine purposes, not a single protein. (All of the specific examples in Livesey relate to whole cells or, in the case of Example 5, an entire virus.) There are no examples of preserving individual proteins, let alone Factor VIII, which is a particularly delicate and unstable protein. This is consistent with the requirement for a suspension of biological nutrient.

In the case of a viral vaccine like the OPV of Example 5, one can probably tolerate some denaturation of proteins, and even the inactivation of some of the virus particles during processing and storage. In the case of the labile functional protein Factor VIII, such denaturation/degradation would not be acceptable.

Example 5, as it does not relate to Factor VIII anyway, appears irrelevant on its face. Nevertheless, what it appears to show is that trehalose is no better protectant than buffer alone (*see* the table at the top of column 24).

Further, applicants find no attempt to explain why one of skill in the art would be motivated to combine Curtis with Livesey absent the teaching of the present invention, or even if the teachings of the present invention are considered. The present invention concerns conditions for stabilizing dried native Factor VIII so that no refrigeration is required during storage. The teachings of Curtis,

to the extent that they can be considered teachings of stabilization conditions of dried compositions at all, relate to a different protein, activated Factor VIII. And Curtis is silent even as to those conditions. The teachings of Livesey do not concern stabilizing Factor VIII, but rather concern cryostabilization of suspensions of biological materials. Applicant is unable to find any suggestion that would motivate one of skill in the art to combine these documents. There is no suggestion for combination in these documents themselves, they do not concern the same problem, and neither is such a high profile document that it would automatically be considered by one of skill in the art.

From the rationale of the rejection, it appears Lee is added as a tertiary document because it discloses the inclusion of calcium chloride for use in lyophilizing Factor VIII. Lee is thus relevant only to claim 23. Since claim 23 is dependent from claim 20 which is not obvious over the art, claim 23 cannot be obvious over the art either.

Double Patenting

The claims have also been rejected as obviousness type double patenting over U.S. 6,649,386 and three co-pending applications: 10/679,723; 09/888,734; and 10/681,948. Terminal Disclaimers with respect to all of these are enclosed.

Conclusion

Curtis is not relevant to the present invention because it is directed to converting native Factor VIII into activated Factor VIII and fails to describe the stabilization conditions of any dried composition, even activated Factor VIII. Even so, Curtis suggests that the dried preparation must be stored at cold temperatures, contrary to the claims presently presented. Livesey is clearly directed to cryostabilization of suspensions of biological materials, not delicate soluble proteins. The inclusion of biological material "comprising" Factor VIII does not mitigate the requirement that a

suspension of biological material be used in Livesey's process. Lee is relevant only to dependent claim 23. No attempt appears to have been made to explain why the skilled practitioner would be motivated to combine the cited documents. Therefore, applicants believe withdrawal of the one outstanding rejection, applied to all claims, is proper.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 559662000102.

Respectfully submitted,

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